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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
09/265,185	3/10/1999	Carson et al.	07340/044002

EXAMINER	
Quang Nguyen	
ART UNIT	**PAPER**
1636	32

DATE MAILED: 3/4/02

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

37 CFR 1.607(b) requires that "[w]hen an applicant seeks an interference with a patent, examination of the application, including any appeal to the Board, shall be conducted with special dispatch within the Patent and Trademark Office.". Therefore, when all the claims presented are rejected the examiner sets a time limit for reply, not less than 30 days, and all subsequent actions, including action of the Board of appeal, are special. Failure by the applicant to reply or appeal within the time limit, will, in the absence of a satisfactory showing, be deemed a disclaimer of the invention claimed.

With respect to the issue of time limit for responding the Office Action mailed January 17, 2002, Applicants' communication letter dated February 13, 2002 has been considered by the Examiner and Applicants' request for one-month extension of the time limit is granted. Accordingly, the time limit for avoiding a disclaimer of the presently claimed invention has been extended to March 17, 2002.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

DAVE T. NGUYEN
PRIMARY EXAMINER

DETAILED ACTION

Applicants' request for extending the time limit for responding the Office Action mailed January 17, 2002 in Paper No. 29 is acknowledged. However, following a personal interview on 03/04/02 for this application with Applicants, for the purpose of clarity and compact prosecution, the Office Action mailed January 17, 2002 in Paper No. 29 has been vacated by the examiner.

Applicants' amendment filed on 11/01/2001 in Paper No. 28 has been entered.

Applicants' request for an interference between the present application and U.S. Patent Nos. 6,207,646 and 6,194,388 is held in abeyance until the pending claims are in conditions for allowance.

Following is a new and complete Office Action for the pending claims 202-204.

Priority

The present application is a continuation of U.S. Serial No. 08/593554 (not 08/593,544 as indicated on page 2 of the amendment filed on 11/01/2001), filed January 30, 1996, now abandoned, which is a continuation-in-part of U.S. Serial No. 08/446,691, filed June 7, 1995, now abandoned, which is a 371 national phase filing of PCT/US94/09661, filed August 25, 1994, which designated the U.S., which is a continuation-in-part of U.S. Serial No. 08/112,440, filed August 26, 1993.

Upon review of the specifications of great-grandparent (U.S Serial No. 08/112,440), grandparent (U.S. Serial No. 08/446,691) and parent (U.S. Serial No. 08/593,554) applications and comparison with the specification of the present

application, it is determined that the pending claims are only entitled to the priority benefit of the filing date of January 30, 1996. When read in light of the present specification, claims 202 and 203 encompass a composition comprising a recombinant antigen and any plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and wherein the immunostimulatory nucleic acid sequence is either already present in the plasmid or it is inserted into the plasmid in any desired copy numbers, including the plasmid pREP7 (see instant specification, page 11, second full paragraph, last paragraph continues to first paragraph on page 12), and that said antigen is produced by a process using the plasmid. Similarly, claim 204 encompasses a method of treating an allergy in a vertebrate utilizing an effective amount of an immunostimulatory nucleic acid comprising the 5'CG3' motif in any plasmid, wherein C is unmethylated, and wherein the immunostimulatory nucleic acid is either already present in the plasmid or it is inserted into the plasmid in any desired copy numbers and an effective amount of a recombinant antigen that is produced by a process using the plasmid. The embodiments of these instant claims are not supported by the specifications of the great-grandparent application U.S. Serial No. 08/112,440, filed August 26, 1993 and the grandparent application U.S. Serial No. 08/446,691, filed June 7, 1995. There is no explicit teachings regarding to any immunostimulatory nucleic acid sequence, let alone an immunostimulatory nucleic acid comprising 5'CG3' or one comprising AACGTT in the aforementioned great-grandparent and grandparent applications. The mere mentioning that "Other preferred plasmid vectors are pREP7 and pREV which are commercially

available from Invitrogen of San Diego, California" (page 23, lines 17-18 in U.S. Serial No. 08/112,440; page 33, lines 1-2, in U.S. Serial No. 08/446,691) is not an indication that at the filing dates of the great-grandparent and grandparent applications, Applicants appreciate or realize the potential usefulness of any immunostimulatory nucleic acid sequence comprising the CpG motif, wherein C is unmethylated, as an adjuvant to stimulate CTL activity or to stimulate production of interferons by lymphocytes as contemplated by the present application (page 10, first paragraph of the present specification). As such, on the basis of the aforementioned great-grandparent and grandparent applications, it is not apparent to one of ordinary skilled artisan that Applicants contemplated specifically to make and use a composition comprising a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' or introducing said immunostimulatory nucleic sequence into any plasmid that is absent of such immunostimulatory nucleic acid sequence at any time period prior to January 30, 1996. Furthermore, there is also no support in the grandparent or the great-grandparent applications for the make and use of any plasmid containing an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' in conjunction or in a combination with an antigen in any form.

Accordingly, the pending claims are only entitled to the priority benefit of the filing date of January 30, 1996 for the reasons set forth above.

Response to Arguments

Applicants' argument related to the priority of the pending claims in the Amendment filed on 11/01/2001 in Paper No. 28 (pages 14-15) have been fully considered.

Applicants argued that "Applicants are entitled to priority benefit of the filing date of U.S. Serial No. 08/112,440, filed August 26, 1993, and U.S. Serial No. 08/446,691, filed June 7, 1995, because both prior applications disclose at least a constructive reduction to practice of the species of claim 203, which species falls within the genus of claim 201". Applicants specifically stated that "The great-grandparent application U.S. Serial No. 08/112,440 describes AACGTT-containing antigen-encoding plasmids that may be used to generate an immune response. An antigen-encoding plasmid based on the vector pREP7, which is a species of claim 202, is described in the instant application on page 26, lines 5-6, the grandparent application U.S. Serial No. 08/446,691, on page 33, lines 1-2, and the great-grandparent application of US. Serial No. 08/112,440, on page 23, lines 17-18 (and in Example I).....This plasmid contains an ampicillin resistance gene, which in turn contains the immunostimulatory CT-containing sequence AACGTT.....Thus, the great-grandparent application (U.S. Serial No. 08/112,440), having a filing date of August 26, 1993, discloses an antigen encoding plasmid having the immunostimulatory sequence AACGTT". Examiner respectfully finds Applicants' argument to be unpersuasive for the following reasons.

There is no explicit teachings regarding to the make and use of any immunostimulatory nucleic acid sequence, let alone an immunostimulatory nucleic acid

comprising 5'CG3' or one comprising AACGTT in the aforementioned great-grandparent and grandparent applications. The mere mentioning that "Other preferred plasmid vectors are pREP7 and pREV which are commercially available from Invitrogen of San Diego, California" (page 23, lines 17-18 in U.S. Serial No. 08/112,440; page 33, lines 1-2, in U.S. Serial No. 08/446,691) is not an indication that at the filing dates of the great-grandparent and grandparent applications, Applicants appreciate or realize the potential usefulness of any immunostimulatory nucleic acid sequence comprising the CpG motif, wherein C is unmethylated, as an adjuvant to stimulate CTL activity or to stimulate production of interferons by lymphocytes as contemplated by the present application (page 10, first paragraph of the present specification). As such, on the basis of the aforementioned great-grandparent and grandparent applications, it is not apparent to one of ordinary skilled artisan that Applicants contemplated specifically to make and use a composition comprising a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' or introducing said immunostimulatory nucleic sequence into any plasmid that is absent of such immunostimulatory nucleic acid sequence at any time period prior to January 30, 1996. The disclosure that the plasmid vector pREP 7 contains an ampicillin resistance gene, which in turn contains the immunostimulatory sequence AACGTT is only made after the filing dates of the great-grandparent and grandparent applications. Moreover, it is also apparent to one of ordinary skilled artisan that Applicants do not contemplate to make and use of any plasmid containing an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' in conjunction or in a combination with an antigen in any form at any time

period prior to January 30, 1996, because there is no support for such teachings in the grandparent and the great-grandparent applications.

Accordingly, the pending claims are only entitled to the priority benefit of the filing date of January 30, 1996 for the reasons set forth above.

To the extent that Applicant's amendment dated 10/31/01 is relevant to the following stated rejections of this instant office action, Applicant's comments in the amendment dated 10-31-01 have been considered by the examiner but they are not found relevant to the examination of the pending claims and thus they are not found persuasive. More importantly, Applicants asserted on page 6 through page 7 that the examiner during the interview dated 10/2/01 agreed that the term "antigen" **cited in claim 6 of an issued patent (6,207,646)** encompasses "an antigen encoded by a nucleic acid such as in a DNA vaccine", and that the claims of the '646 patent are obvious variants of the pending claims of this instant application. However, there is no such agreement *per se* of record, nor did the examiner agree to any issue in regard to obvious variants from the claims of the '646 patent. While the examiner acknowledged that the discussion of the claims of the '646 patent including the term "antigen" cited in claims 6 and 10 of the '646 patent has been raised by Applicants, and Applicants did present their interpretations of the claims and the terms cited in the claims of the issued patent during the interview. However, there was no agreement by the examiner during the interview of any issue with respect to the pending claims of this instant application, particularly since the examiner's examination of the pending claims of the as-filed application on the basis of applicants' disclosure has not been officially conducted prior

to the interview. Furthermore, it is not apparent how the issued claims of the '646 patent are relevant to the examination of the pending claims of this as-filed application because each application is treated on its own merits and because the pending claims are still under examination and therefore they are not in conditions for any discussion and/or agreement of a potential interference, as suggested by applicants in the amendment dated 10/31/01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 204 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing an antigen specific IgE production or for increasing stimulation of an antigen specific TH 1 response in a mammal comprising intradermal injection in said mammal an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising AACGTT, wherein C is unmethylated, and an effective amount of an antigen, wherein said antigen is produced by a process using the plasmid, does not reasonably provide enablement for other embodiments of the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

In light of the as-filed specification, the claim as written is directed to a method of treating an allergy in any vertebrate (e.g., frog, chicken, fish, mammal) comprising administering to the vertebrate an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and an effective amount of a recombinant antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is produced by a process using the plasmid.

With respect to the nature of the instant claim, the specification teaches by exemplification showing that mice that received intradermally the pCMV-lacZ vector containing two copies of the immunostimulatory polynucleotide with the sequence AACGTT within the AmpR gene of the vector produced high titers of IgG 2A antibodies (serological markers for a TH1 type immune response), whereas mice injected intradermally with β-galactosidase produced high titers of IgG 1 antibodies (serological markers for a TH2 type immune response). The same groups of mice were boosted with 0.5 μg of β-galactosidase intradermally, boosting intradermal pCMV-lacZ primed mice with the enzyme induced about 10-fold rise in IgG 2A antibody responses,

whereas it did not stimulate an IgG 1 response. It is noted that boosting intradermal β-galactosidase primed mice with the enzyme induced a significant rise in IgG 1 responses without any stimulation of an IgG 2A response, and that boosting of intramuscular pCMV-lacZ primed mice with the enzyme has little induction in either IgG 2A or IgG 1 responses (See Figs. 15 and 16). The specification further teaches that upon an intraperitoneal challenge with β-galactosidase 14 weeks after the initial immunization, anti-β-galactosidase IgE levels in intradermal pCMV-lacZ mice were consistently low after boosting as before boosting, while protein injected mice developed high levels of anti-β-galactosidase IgE, especially after the first antigen boosting injection (Fig. 17). Furthermore, Applicants teach that CTL activity in cultures of cells from the pCMV-lacZ injected mice increased from about 18% activity to nearly 100% activity, whereas the CTL activity in cell cultures from the pKCB-lacZ (without the immunostimulatory polynucleotide) or control injected mice barely exceeded 20% lytic activity. An increase in CTL activity was however observed in cell cultures from pKCB-lacZ & pUC-19 (pUC-19 plasmid vector includes the AmpR gene) co-injected mice.

The above evidence has been noted and considered. However, the above evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

The breadth of the instant claim encompasses a method for attaining a broad range of therapeutic effects ranging from reducing or alleviating to complete abolishment or preventing symptoms associated with an allergy in a vertebrate (within the scope of treating) comprising the utilization of an effective amount of an

immunostimulatory nucleic acid comprising 5'CG3' in a plasmid of the presently claimed invention. The present specification is not enabled for such a broadly claimed invention. There is no reasonable correlation between an apparent lack of IgG 1 response stimulation and low levels of anti-β-galactosidase IgE levels observed in intradermal pCMV-lacZ primed mice after boosting with β-galactosidase with the prevention or abolishment of symptoms associated with any allergy in a vertebrate as encompassed by the scope of the instant claim. This is because after boosting with β-galactosidase, IgG 1 response was still present in the intradermal pCMV-lacZ primed mice, and although low levels of anti-β-galactosidase IgE were observed in the same mice, these levels are nevertheless represent a significant stimulation with respect to the pre-boosting anti-β-galactosidase IgE level (see Fig. 17). Moreover, splenocytes removed from pCMV-LacZ treated mice and challenged *in vitro* with β-galactosidase antigen are still capable of producing enhanced levels of IFN-γ and IL-4 in comparison with the splenocytes removed from the negative control pKCB-LacZ treated mice (see Example IX). The cytokine IL-4 is well known for turning on the IgE-producing cells and for development of the TH2 cells. It is also not apparent from the instant specification that an effective mucosal immunity has been established or achieved in a vertebrate by the presently claimed invention since the mucosal immunity is important to prevent pathogen entry, for this instance allergens causing allergy to yield the prophylactic or preventive therapeutic effects contemplated by Applicants. Even several years after the effective filing date of the present application, the role of CpG immunostimulatory sequence in regulating host immune responses is still not clearly understood as

exemplified by the teachings of McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999). McCluskie et al. stated that "[I]t is possible that the CpG content of the vector may influence whether immune responses are biased towards a Th1- or Th2-type and explain, at least in part, why different plasmids induce predominantly Th1, Th2, or mixed Th1/Th2 responses when naked DNA is delivered to the lungs" (page 313, col. 2, first paragraph). McCluskie et al. further noted that various other factors such as the antigen, the dose of antigen, the route and method of DNA administration, the coexpression of cytokines and the presence or absence of other adjuvant may also involve in determining whether a Th1 or Th2 response predominates after mucosal immunization. As such, it is uncertain whether the scope of therapeutic effects contemplated by Applicants for the claimed method could be obtained by a skilled artisan without undue experimentation.

The instant claim encompasses the utilization of an effective amount of any immunostimulatory nucleic acid in a plasmid as long as said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated to treat an allergy in a vertebrate. The instant specification is not enabled for such a broadly claimed invention. Apart from the exemplification showing the development of β-galactosidase specific TH1 response to the pCMV-lacZ plasmid containing two copies of the nucleic acid sequence comprising the palindromic sequence AACGTT (SEQ ID NO: 1), with concomitant suppression of anti-β-galactosidase IgE production in a mouse model, the specification fails to teach a representative number of immunostimulatory sequences that can induce the same immunostimulatory activity as that mediated by SEQ ID NO: 1. It should be

noted that the mere possession of the CpG motif in a polynucleotide sequence is not sufficient for inducing the desired immune responses contemplated by Applicants. This is supported by various teachings in the art at the effective filing date of the present application. For example, Kuramoto et al. (Jpn. J. Cancer Res. 83:1128-1131, 1992; IDS) teach that the relationship between the sequence and the activity of the palindrome is not very clear at present, and that some oligonucleotides with a palindromic sequence including the 5'CG3' do not have immunoenhancing effects, and that "studies are necessary on the target molecule(s) of the palindromic sequences" (page 1129, col. 2, third full paragraph). Branda et al. (J. Lab. Clin. Med. 128:329-338, 1996; IDS) stated that "inspection of the oligodeoxynucelotides known to enhance B cell function (Table 1) fails to show any important homologies", and that "examination of Table 1 indicates that some oligomers that stimulate B cells do not have the CpG motif (see reference 16), whereas others that contain CpG dinucleotides do not activate lymphocytes (see references 22, 23, 24, and 26)" (page 336, col. 2). In addition, Table I of Branda et al. further indicates that oligonucleotides containing clusters of direct repeats of CG dinucleotides exhibit no immune-neutralizing and/or immune-inhibitory effects (items 10 and 13, for examples). Similarly, Ballas et al. (J. Immunol. 157:1840-1845, 1996; IDS) stated that "While necessary, however, a CpG motif was not sufficient for NK cell induction. Instead, there appeared to be stringent requirements for the immediate flanking bases at the 5' and 3' ends as well as for flanking sequences outside the immediate 5' and 3' bases" (See abstract). Furthermore, Weiner et al. (PNAS 94:10833-10837, 1997; IDS) reaffirmed the doubts by teaching that "the

molecular mechanism responsible for CpG ODN-induced immunostimulation, and an explanation for why different CpG ODN have different effects remain unclear and need to be elucidated" (page 10836, col. 2). Even in a review article several years after the effective filing date, questions such as "How many and what type of CpG motifs will be optimal for enhancing DNA vaccine efficacy?", "Does it matter whether these CpG motifs are cloned into the vector or given as oligonucleotides?", and "Is the location of CpG motifs in a DNA vaccine important?" are still needed to be investigated (Krieg et al., Trends in Microbiology 6:23-27, 1998; page 25, col. 2, last paragraph; IDS). Thus, it is not apparent as to how one skilled in the art at the effective filing date of the present application would be able to identify a common mechanism or structural feature which is found in a broad genus of immunostimulatory nucleic acid contemplated by Applicants to treat an allergy in a vertebrate without undue experimentation.

Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The instant claim also encompasses any route of delivering an effective amount of an immunostimulatory nucleic acid of the present invention into a vertebrate to treat an allergy in said vertebrate. The instant specification is not enabled for such a broadly

claimed invention. This is because as clearly demonstrated by the present application that boosting of intramuscular pCMV-lacZ primed mice with the enzyme does not enhance any IgG 2A response whose level is even lower than that induced in the β-galactosidase primed mice (See Fig. 15). Boosting intramuscular pCMV-lacZ primed mice with the enzyme also does not suppress the induction of IgG 1 response, but rather a slight stimulation was observed even though the stimulation level is much less than those obtained for intradermal pCMV-lacZ and β-galactosidase primed (See Fig. 16). Moreover, even in the absence of a subsequent boosting with the enzyme, the level of IgG 2A response to β-galactosidase is not stimulated upon intramuscular injection of pCMV-lacZ, whereas a significantly enhanced IgG 2A response was clearly observed for mice injected with β-galactosidase (see Fig. 13). Thus, it is apparent that intramuscular administration pCMV-lacZ plasmid into a mouse does not induce the desired selective induction of Th 1 response that is capable of providing the therapeutic effects contemplated by Applicants for treating an allergy. Nor does the instant specification provide support for any other routes of delivering into a vertebrate a plasmid containing an immunostimulatory nucleic acid other than the intradermal injection route that are capable of eliciting the desired selective induction of a Th1 response in a vertebrate upon challenge with an allergen. With the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

With respect to the breadth of the claim encompassing treating an allergy in a vertebrate including human, mouse, monkey, chicken, frog and fishes among others,

the instant specification is not enabled for such a broadly claimed invention. Apart from the mouse model exemplification, it is unclear whether the desired selective induction of TH1 response that is beneficial for treating an allergy could be obtained in numerous species encompassed within the broad genus of a vertebrate in the claimed method. It is also unclear whether the immune components of a fish or a frog would react to an allergen in a similar manner as those of a mammal, and similarly whether an induction of the desired TH1 response would also be induced by the immunostimulatory nucleic acid of the presently claimed invention to yield the contemplated therapeutic effects. An extensive search for the prior art at the effective filing date of the present application revealed that little has been known about the immune responses in species such as frog, fish or chicken, let alone on the preferential induction in TH1 immune response for treating allergy in these species. As such, the contemplated therapeutic results for a broad number species encompassed by the scope of the present application would not be predictive. Thus, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the method as claimed. Furthermore, regarding to the breadth for treating an allergy in any vertebrate in the method as claimed, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art and DNA vaccination, coupled with the breadth of the claim, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

The Declaration of Dr. Eyal Raz filed under 37 C.F.R. 1.132 in the Amendment A dated 04/21/1999 in Paper No. 8 is acknowledged, and it has been fully considered. However, the additional data supplied in the Declaration do not address the issues set forth above. Examiner would also like to note that the data related to an antigen/ISS-ODN conjugate in the submitted Declaration are not relevant because the instant specification does not provide support for the make and use of such a composition.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 204 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 204, the phrase "an effective amount of an immunostimulatory nucleic acid in a plasmid,....., and an effective amount of an antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is encoded in the plasmid" is unclear. A plasmid may comprise a DNA sequence encoding an antigen, wherein said DNA sequence is operably linked to a promoter for the expression of an effective amount of said antigen. In Amendment C filed 10/31/01 (pages 14-15), Applicants argued that an AACGTT-containing antigen-encoding plasmid (one that is based on the vector pREP7) is a species of a composition of the presently claimed invention for claiming the priority of the great-grand parent and grandparent applications. However, an effective amount of an antigen (a protein or a peptide) is not a part or a portion of a plasmid (a nucleic acid molecule) being administered into a vertebrate as the claim suggests because a protein or a peptide is chemically and structurally distinct from a nucleic acid molecule. Clarification is requested regarding whether Applicants intend to claim a method wherein an antigen is a distinct component from a plasmid containing an immunostimulatory nucleic acid comprising 5'CG3' or it is a part of said plasmid (being encoded by the plasmid).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 202 is rejected under 35 U.S.C. 102(e) as being anticipated by Davis (U.S. Patent No. 5,780,448 with the effective filing date of November 07, 1995) as evidenced by Krieg et al. ((U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS).

The claim is drawn to a composition comprising: a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is produced by a process using the plasmid.

Davis teaches the preparation of a composition for inducing an immune response in finfish comprising an expression vector having an expression control sequence capable of directing expression in finfish of at least one immunogenic polypeptide and a polypeptide encoding DNA sequence encoding at least one immunogenic polyeptide from a fish pathogen (an antigen), wherein the vector additionally comprises an immunostimulatory unmethylated CpG motif (see col. 4, lines 10-30; col. 11, lines 8-13 and the claims). Davis also teaches that multiple CpG motifs may be inserted into the non-coding region of the expression vector (col. 7, lines 23-25), and that expression

vector includes purified plasmid DNA that is dissolved in an aqueous solution or in a formulation such as cationic liposomes, fluorocarbon emulsions, gold particles, biodegradable microspheres or cationic polymers which are pharmaceutically acceptable carriers (col. 8, lines 27-35). Davis further teach that the aforementioned pharmaceutical composition further comprising a second DNA vaccine, an adjuvant, a recombinant protein (an antigen), a transfection reagent, or some combination thereof (col. 9, lines 13-20). At the effective filing date of the present application, several immunostimulatory nucleic acid sequences having the CpG motifs have been shown to activate the immune system, including the sequence comprising AACGTT as evidenced by the teachings of Krieg et al. (see Table 1 and the claims).

Therefore, the instant claim is anticipated by Davis as evidenced by Krieg et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 202 and 203 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) in view of Davis (U.S. Patent No. 5,780,448 with the effective filing date of November 07, 1995).

The claims are drawn to a composition comprising: a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is produced by a process using the plasmid; the same wherein the plasmid is pREP7 encoding an antigen.

Krieg et al. disclose various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising AACGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teach that the immunostimulatory oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. do not teach specifically the use of an immunostimulatory unmethylated CpG motif or an immunostimulatory

sequence comprising AACGTT in the form of a plasmid or more specifically in the plasmid pREP7 encoding an antigen.

At the effective filing date of the present application (January 30, 1996), Davis teaches that since copies of CpG motifs in DNA expression vectors act as adjuvants facilitating the induction of an immune response against an expression protein, multiple CpG motifs may be inserted into the non-coding region of an expression vector containing a sequence encoding an antigen (col. 7, lines 18-48; col. 11, lines 1-16). Davis further discloses that the antigen expressing vectors can be utilized concurrently with an antigen-based vaccine such as a recombinant protein or whole-killed vaccine (col. 8, lines 16-22).

Accordingly, it would have been obvious for one of ordinary skilled artisan to modify the composition taught by Krieg et al. by specifically incorporating one or more copies of the immunostimulatory nucleic acid sequence having the unmethylated CpG motifs, including one that comprises the sequence AACGTT taught by Krieg et al. in the non-coding region of an expression plasmid vector as taught by Davis to use it as an adjuvant for a vaccine or an antigen in a pharmaceutically acceptable carrier or for an antigen encoded in the expression plasmid vector. One of ordinary skilled artisan would have been motivated to carry out the above modification because both Krieg et al. and Davis teach that unmethylated CpG dinucleotide motifs present in plasmid vectors or in free oligonucletides act as adjuvants to boost a mammal's immune response to effect better response from an antigen-based vaccine such as a recombinant protein or whole-killed vaccine or a plasmid DNA vaccine comprise a sequence encoding an antigen.

Furthermore, it would also have been obvious for one of ordinary skilled artisan to use the plasmid pREP7 as an expression vector in the composition because of a designer's choice since the plasmid is publicly available from Invitrogen (Carlsbad, CA 92008 USA; Tel. No. 1-800-955-6288). Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 202 and 203 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) in view of Applicants' admission of record (Amendment C filed 10/31/01 in Paper No. 28, page 8, second last paragraph and page 9, second paragraph).

Krieg et al. disclose various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising AACGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teach that the immunostimulatory oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. do not teach specifically the use of an immunostimulatory unmethylated CpG motif or an immunostimulatory sequence comprising AACGTT in the form of a plasmid or more specifically in the plasmid pREP7 encoding an antigen.

However, Applicants have submitted on record that a plasmid is an obvious polynucleotide species in view of a polynucleotide of at least 8 nucleotides (the immunostimulatory oligonucleotides taught by Krieg et al. are in the range of between 2 to 100 base pairs, with a preferred embodiment between 8 to 40 base pairs in size), and that administering an antigen is obvious in view of administering an antigen encoded by a plasmid (see Amendment C in Paper No. 28; page 8, second last paragraph; page 9, second paragraph).

Accordingly, it would have been obvious for one of ordinary skilled artisan to modify the composition taught by Krieg et al. by introducing the immunostimulatory nucleic acid sequences having the unmethylated CpG motifs, including one that comprises the sequence AACGTT taught by Krieg et al. into a plasmid vector to use it as an adjuvant for a vaccine or an antigen in a pharmaceutically acceptable carrier. Furthermore, it would also have been obvious for one of ordinary skilled artisan to use the plasmid pREP7 as a vector in the modified composition because of a designer's choice since the plasmid is publicly available from Invitrogen (Carlsbad, CA 92008 USA; Tel. No. 1-800-955-6288). Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 204 is rejected under 35 U.S.C. 103(a) as being unpatentable over Terr (Allergy desensitization, pages 739-743, 1992; IDS) in view of Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) and Davis (U.S. Patent No. 5,780,448 with the effective filing date of November 07, 1995).

The claim is directed to a method of treating an allergy in a vertebrate, comprising administering to the vertebrate an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and an effective amount of an antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is produced by a process using the plasmid.

Terr teaches that allergens (an allergen is an antigen that is capable of inducing an allergic reaction; Dictionary of Science and Technology, Morris, ed., 1994; IDS) are routinely injected subcutaneously into a patient for the purpose or reducing the allergic response in a well-known treatment called allergen immunotherapy (most often used in IgE antibody-mediated diseases). Moreover, Terr has also taught that adjuvants such as incomplete Freud's adjuvant or alum were used together with allergens in an allergen immunotherapy in an attempt to improve the treatment efficacy via enhancing the immune response, or reducing the number of injections required (page 743, see section titled "desensitization with modified allergens"). However, Terr noted that the form of therapy utilizing incomplete Freud's adjuvant was abandoned because of concern about potential carcinogenicity and that alum-absorbed allergens have had limited acceptance in practice. Terr does not teach the use of any immunostimulatory nucleic acid comprising 5'CG3' in a plasmid as an adjuvant.

At the effective filing date of the present application, Krieg et al. teach a composition comprising an immunostimulatory oligonucleotide that contains a consensus mitogenic CpG motif represented by the formula: 5'-$X_1X_2CGX_3X_4$-3', wherein

C and G are unmethylated, X_1, X_2, X_3 and X_4 are nucleotides (including an an immunostimulatory oligonucleotide comprising AACGTT), and an antigen (col. 6-7 and the claims). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Krieg et al. specifically teach that the immunostimulatory oligonucleotides are used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. also teach a method for enhancing an immune response in a mammal using the composition disclosed above (see the entire patent and claim 21). Additionally, Davis teaches that since copies of CpG motifs in DNA expression vectors act as adjuvants facilitating the induction of an immune response against an expression protein, multiple CpG motifs may be inserted into the non-coding region of an expression vector containing a sequence encoding an antigen (col. 7, lines 18-48; col. 11, lines 1-16). Davis further discloses that the antigen expressing vectors can be utilized concurrently with an antigen-based vaccine such as a recombinant protein or whole-killed vaccine (col. 8, lines 16-22).

Accordingly, it would have been obvious for an ordinary skilled artisan, particularly for a physician in the field of allergy, to modify an allergen immunotherapy method taught by Terr by injecting subcutaneously into a patient allergens along with an effective amount of immunostimulatory nucleic acid comprising the sequence AACGTT in the form of a plasmid (instead of oligonucleotides) for reducing the allergic response

in a patient. One of ordinary skilled artisan would have been motivated to carry out the above modifications because both Krieg et al. and Davis already teach that the CpG motifs (including the sequence AACGTT) in free oligonucleotides or in DNA expression vectors can act as adjuvants facilitating the induction of an immune response against a co-administered antigen or an expressed antigen encoded in an expression plasmid. Furthermore, one of ordinary skilled artisan would also have been motivated to use the immunostimulatory nucleic acid sequence AAGCTT in conjunction with co-administered allergens in order to enhance the immune response to improve the effectiveness of allergen immunotherapy or reduced the number of injections as taught by Terr, and since CpG motifs including the AAGCTT have been shown to enhance at least an immune response in a mammal as taught by Krieg et al. or in a fish as taught by Davis, and also to avoid the potential carcinogenicity caused by the use of incomplete Freund's adjuvant in allergen immunotherapy.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 204 is rejected under 35 U.S.C. 103(a) as being unpatentable over Terr (Allergy desensitization, pages 739-743, 1992; IDS) in view of Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) and Applicants' admission of record (Amendment C filed 10/31/01 in Paper No. 28, page 8, second last paragraph and page 9, second paragraph).

Terr teaches that allergens (an allergen is an antigen that is capable of inducing an allergic reaction; Dictionary of Science and Technology, Morris, ed., 1994; IDS) are routinely injected subcutaneously into a patient for the purpose or reducing the allergic response in a well-known treatment called allergen immunotherapy (most often used in IgE antibody-mediated diseases). Moreover, Terr has also taught that adjuvants such as incomplete Freud's adjuvant or alum were used together with allergens in an allergen immunotherapy in an attempt to improve the treatment efficacy via enhancing the immune response, or reducing the number of injections required (page 743, see section titled "desensitization with modified allergens"). However, Terr noted that the form of therapy utilizing incomplete Freud's adjuvant was abandoned because of concern about potential carcinogenicity and that alum-absorbed allergens have had limited acceptance in practice. Terr does not teach the use of any immunostimulatory nucleic acid comprising 5'CG3' in a plasmid as an adjuvant.

At the effective filing date of the present application, Krieg et al. teach a composition comprising an immunostimulatory oligonucleotide that contains a consensus mitogenic CpG motif represented by the formula: 5'-$X_1X_2CGX_3X_4$-3', wherein C and G are unmethylated, X_1, X_2, X_3 and X_4 are nucleotides (including an an immunostimulatory oligonucleotide comprising AACGTT), and an antigen (col. 6-7 and the claims). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Krieg et al. specifically teach that the immunostimulatory oligonucleotides are used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to

boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. also teach a method for enhancing an immune response in a mammal using the composition disclosed above (see the entire patent and claim 21). Additionally, Applicants have submitted on record that a plasmid is an obvious polynucleotide species in view of a polynucleotide of at least 8 nucleotides (the immunostimulatory oligonucleotides taught by Krieg et al. are in the range of between 2 to 100 base pairs, with a preferred embodiment between 8 to 40 base pairs in size), and that administering an antigen is obvious in view of administering an antigen encoded by a plasmid (see Amendment C in Paper No. 28; page 8, second last paragraph; page 9, second paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan, particularly for a physician in the field of allergy, to modify an allergen immunotherapy method taught by Terr by injecting subcutaneously into a patient allergens along with an effective amount of immunostimulatory nucleic acid comprising the sequence AACGTT in the form of a plasmid (instead of oligonucleotides) for reducing the allergic response in a patient. One of ordinary skilled artisan would have been motivated to carry out the above modifications because Krieg et al. already teaches that the CpG motifs (including the sequence AACGTT) in free oligonucleotides (8-40 nucleotide in size in a preferred embodiment) or in DNA expression vectors (an obvious variant for a polynucleotide of at least 8 nucleotides) can act as adjuvants to facilitate the induction of an immune response against a co-administered antigen or an expressed antigen encoded in an expression plasmid (an obvious variant for an antigen). Furthermore, one of ordinary

skilled artisan would also have been motivated to use the immunostimulatory nucleic acid sequence AAGCTT in conjunction with co-administered allergens in order to enhance the immune response to improve the effectiveness of allergen immunotherapy or reduced the number of injections as taught by Terr, and since CpG motifs including the AAGCTT have been shown to enhance at least an immune response in a mammal as taught by Krieg et al., and also to avoid the potential carcinogenicity caused by the use of incomplete Freund's adjuvant in allergen immunotherapy.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

37 CFR 1.607(b) requires that "[w]hen an applicant seeks an interference with a patent, examination of the application, including any appeal to the Board, shall be conducted with special dispatch within the Patent and Trademark Office.". Therefore, when all the claims presented are rejected the examiner sets a time limit for reply, not less than 30 days, and all subsequent actions, including action of the Board of appeal, are special. Failure by the applicant to reply or appeal within the time limit, will, in the absence of a satisfactory showing, be deemed a disclaimer of the invention claimed. **A time limit for response to this Office Action is set to expire ONE MONTH from the date of this action.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER